EXHIBIT 11

1: Jpn J Pharmacol. 2000 Mar;82(3):188-98.

Antiplatelet and antithrombotic effects of a novel selective phosphodiesterase 3 inhibitor, NSP-513, in mice and rats.

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We investigated the effects of NSP-513, (R)-4,5-dihydro-5-methyl-6-[4-(2-propyl-3-oxo-1-cyclohexenyl)amino] phenyl-3 (2H)-pyridazinone, on phosphodiesterase (PDE) isozyme activities, in vitro platelet aggregation and in vivo thrombus formation. NSP-513 selectively inhibited human platelet PDE 3 isozyme with an IC50 value of 0.039 microM. In an in vitro human platelet aggregation assay, the IC50 values (microM) of NSP-513 for platelet aggregation induced by collagen, U-46619, arachidonic acid, adenosine diphosphate (ADP), epinephrine and thrombin were 0.31, 0.25, 0.082, 0.66, 0.23 and 0.73, respectively. In a mouse pulmonary thromboembolism model, orally administered NSP-513 showed in vivo antithrombotic effects that were 320 to 470 times more potent than those of cilostazol. In a rat carotid arterial thrombosis model, intraduodenally administered NSP-513 (0.1 mg/kg), cilostazol (30 mg/kg) and aspirin (30 mg/kg) reduced thrombus formation by 75%, 66% and 48%, respectively. However, intravenously administered dipyridamole (10 mg/kg) did not significantly prevent thrombus formation. These results demonstrate that NSP-513 has the potential to prevent not only in vitro platelet aggregation but also in vivo thrombus formation and indicate that the highly selective PDE 3 inhibitory effect of NSP-513 may make this compound useful for assessing the physiological role of PDE 3.

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